DECLARATION

I, Jane Roberta Mann, B.A., a Translator, of Frank B. Dehn & Co., 59 St Aldates, Oxford OX1 1ST, England, do declare that I have a competent knowledge of the English and German languages and that the document that is annexed hereto is a true and accurate translation of the German text of the U.S. Provisional Application Serial No. 60/471,675 filed May 19, 2003.

I further declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true.

I acknowledge that wilful false statements and the like are punishable by fine or imprisonment, or both [18 U.S.C. 1001] and may jeopardize the validity of the application or any patent issuing therefrom.

Signed this 11th day of March, 2004

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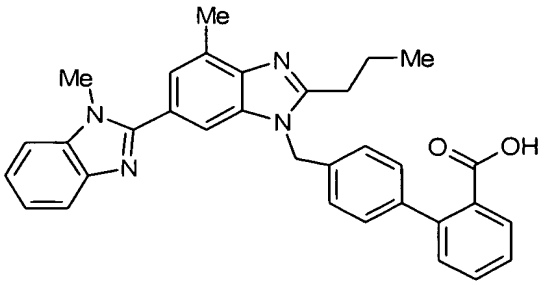
Pharmaceutical formulation of the telmisartan sodium salt

The invention relates to a pharmaceutical formulation of the crystalline sodium salt of 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid (telmisartan), as well as processes for the preparation thereof.

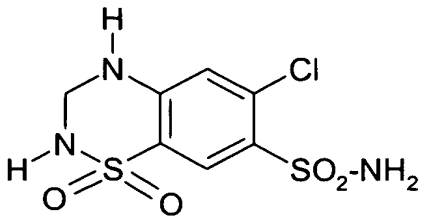
Background to the invention

The compound telmisartan is known from European Patent EP 502 314 B1 and has the following chemical structure:



Telmisartan, and the physiologically acceptable salts thereof, have valuable pharmacological properties. Telmisartan is an angiotensin antagonist, particularly an angiotensin-II-antagonist which by virtue of its pharmacological properties may be used for example to treat hypertension and cardiac insufficiency, to treat ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), to prevent the progression of cardiac insufficiency after myocardial infarct, to treat diabetic neuropathy, glaucoma, gastrointestinal diseases and bladder diseases. Other possible therapeutic applications can be found in EP 502314 B1 and WO 02/15891, the contents of which are hereby referred to.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic which is taken orally to treat oedema and high blood pressure. The chemical name of HCTZ is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazin-7-sulphonamide-1,1-dioxide and the compound is described by the following structural formula:



Telmisartan is commercially obtainable under the brand name Micardis®, while a combination of telmisartan with hydrochlorothiazide (HCTZ) is commercially obtainable under the brand name Micardis Plus®. Starting from the free acid of telmisartan, these formulations are produced by a complex spray drying process. Because of the limited solubility of the free acid, less complex methods of preparing an alternative preparation are difficult to achieve.

The aim of the present invention is to provide telmisartan in a form which enables a formulation of this active substance to be prepared in a less complex form. It has to be borne in mind that generally the production of a composition containing a pharmaceutically active substance is dependent on various parameters which are linked to the nature of the active ingredient itself. Without being tied thereto, examples of these parameters are the stability of effect of the starting material under different environmental conditions, the stability during the manufacture of the pharmaceutical formulation and the stability in the final compositions of the pharmaceutical preparation. The pharmaceutically active substance used to prepare the above mentioned pharmaceutical composition should be as pure as possible. At the same time its stability on long-term storage must be guaranteed under various environmental conditions. This is absolutely essential, in order to prevent pharmaceutical compositions being used which contain, in addition to the active substance proper, breakdown products thereof. In such a case the content of active substance present in a preparation produced therefrom may be less than the specified amount.

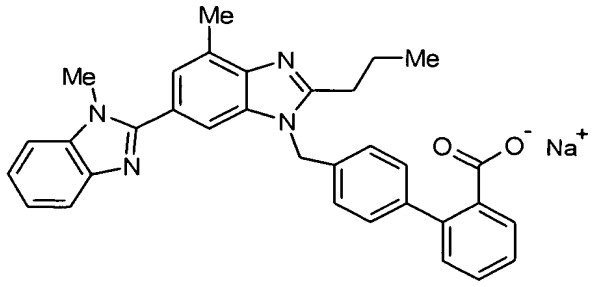
Another aspect which is important in the production of solid preparations is that the active substance should have the most stable possible crystalline morphology for the pharmaceutical quality of a medicinal formulation. If this is not the case, the morphology of the active substance may change in certain

circumstances under the conditions of manufacture of the preparation. Such a change may in turn affect the reproducibility of the manufacturing process and thus lead to final formulations which do not meet the high quality requirements imposed on pharmaceutical formulations. To this extent it should generally be borne in mind that any change to the solid state of a pharmaceutical composition which can improve its physical and chemical stability gives a significant advantage over less stable forms of the same drug.

The object of the invention is thus to provide a new pharmaceutical composition containing a stable form of telmisartan which complies with the above mentioned stringent requirements imposed on a pharmaceutically active substance.

Detailed description of the invention

Surprisingly, it has been found that telmisartan can be obtained in crystalline form, in the form of its sodium salt of formula **1**



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By a suitable choice of manufacturing conditions, the polymorphic form of the crystalline sodium salt which meets the requirements mentioned above can be obtained selectively.

This crystalline form of the sodium salt of telmisartan is characterised by a melting point of T=245 ± 5°C (determined by DSC=Differential Scanning Calorimetry; heating rate: 10 K/min).

The following Table 1 summarises the data obtained in a spectroscopic analysis of the salt:

Table 1:

2 Θ [°]	d [Å]	rel. intensity [%]	2 Θ [°]	d [Å]	rel. intensity [%]
3.54	24.96	7	13.17	6.72	7
4.21	20.95	100	13.68	6.47	7
4.45	19.83	20	14.36	6.16	10
4.98	17.72	54	14.98	5.91	13
5.69	15.52	8	15.51	5.71	14
6.32	13.97	34	15.70	5.64	12
6.48	13.63	35	16.21	5.46	8
7.12	12.41	12	17.09	5.18	10
7.49	11.80	11	17.48	5.07	9
8.08	10.93	4	18.10	4.90	9
8.49	10.41	6	19.18	4.62	11
8.96	9.86	7	19.43	4.56	13
9.50	9.31	5	19.95	4.45	11
10.19	8.68	5	20.89	4.25	11
10.80	8.18	8	21.29	4.17	10
11.16	7.92	18	22.19	4.00	9
11.88	7.44	7	23.07	3.85	10
12.51	7.07	7	23.76	3.74	9
12.79	6.92	11	24.43	3.64	8

In the above Table the value "2 Θ [°]" denotes the angle of diffraction in degrees and the value "d [Å]" denotes the lattice plane spacings determined in Å.

According to the findings given in Table 1, the crystalline telmisartan sodium salt is characterised in that in the X-ray powder diagram it has the characteristic values d= 20.95 Å, 17.72 Å, 13.97 Å and 13.63 Å, *inter alia*.

The X-ray powder diagrams were recorded within the scope of the present invention using a Bruker D8 Advanced with an SSD (= site-sensitive detector) (CuK_α - radiation, = 1.5418 Å, 30 kV, 40 mA).

The crystalline sodium salt of telmisartan according to the invention may also be present in the form of the solvates and hydrates thereof, preferably in the form of the hydrates, most preferably in the form of the hemihydrate thereof.

In another aspect, the present invention relates to a method of producing the crystalline sodium salt of telmisartan according to the invention. The starting material used to prepare the crystalline sodium salt of telmisartan according to the invention may be the free acid of telmisartan, which may be obtained by methods known in the art (e.g. according to EP 502314 A1).

To prepare the crystalline sodium salt according to the invention the free acid of telmisartan is taken up in a suitable solvent, preferably in an organic aprotic solvent, most preferably in an organic, aprotic and non-polar solvent. The solvents used according to the invention are most preferably toluene, chloroform, dichloromethane, tetrahydrofuran, diethylether, diisopropylether, methyl-tert. butylether, acetone, methylisobutylketone, benzene or acetonitrile, of which toluene, benzene and methylisobutylketone are particularly preferred. Of outstanding importance according to the invention is toluene as solvent.

As a rule, between 0.5 and 5 ml, preferably between 1 and 3 ml, most preferably between 1.5 and 2.5 ml of the above mentioned solvent are used per gram of the free acid of telmisartan.

A suitable sodium salt is then added as a base to this solution or suspension. Suitable sodium salts within the scope of the present invention include sodium hydroxide, sodium hydride, sodium carbonate, sodium hydrogen carbonate or sodium alkoxides. By sodium alkoxides are meant the sodium salts which are formed with lower alcohols, preferably with alcohols selected from among methanol, ethanol, isopropanol, n-propanol, tert-butanol, sec.-butanol, isobutanol, n-butanol and tert.-amylalcohol. Of particular interest according to the invention are sodium salts selected from among sodium hydroxide, sodium hydride, sodium ethoxide and sodium methoxide; of these, sodium hydroxide and sodium methoxide are of particular importance according to the invention. The above mentioned sodium salts may be added to the reaction mixture as solids. However, in the case of sodium hydroxide this is preferably added in the form of aqueous solutions. It is particularly preferable to use

concentrated aqueous solutions of sodium hydroxide. For example, sodium hydroxide solution may be used in a concentration of about 45 wt.-%. The amount of sodium salt to be used naturally depends on the amount of free acid telmisartan used. According to the invention at least 1 mol of sodium salt has to be added per mol of telmisartan. It is also possible according to the invention to add an excess of sodium salt. Preferably, 1-2.5, more preferably 1-2, most preferably 1-1.5 mol of sodium salt are added per mol of the acid telmisartan used.

If sodium hydroxide is used as the sodium salt and this is added in the form of an aqueous solution, according to a preferred embodiment of the process according to the invention, it may be helpful in some cases to add a water-miscible organic solvent. This is preferably selected from among methanol, ethanol, isopropanol, acetone, tetrahydrofuran, tert.-butanol, 2-butanol, butanol, glycol, ethyldiglycol, 1,3-butanediol, 1,4-butanediol, tert.-amylalcohol, acetonitrile, nitromethane, formamide, dimethylformamide, N-methylpyrrolidinone, dimethylsulphoxide, dimethylacetamide, nitroethane and methoxy-2-propanol, of which the above mentioned alcohols are particularly significant. It is particularly preferred, within the scope of the process according to the invention, to use methanol or ethanol, above all ethanol. Preferably, between 50 and 500 ml, more preferably between 100 and 400 ml, most preferably between 200 and 350 ml of this solvent are used per mol of telmisartan used, according to the invention.

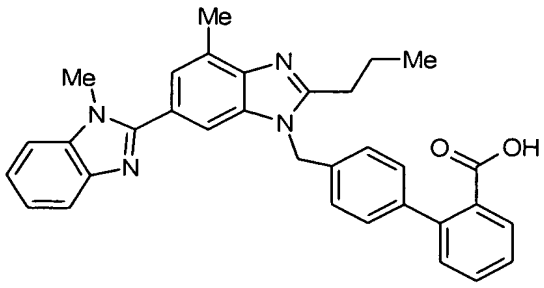
Then the reaction mixture may be heated to speed up the progress of the reaction. Preferably, the reaction mixture is heated to a temperature of >40°C, most preferably to over 60°C, with thorough mixing. The maximum temperature which may be selected is naturally determined by the boiling temperature of the solvents used. If the solvents preferred according to the invention are used, the mixture is preferably heated to over 70°C. This heating is generally carried out for a period of from 15 minutes to 2 hours, preferably between 20 minutes and one hour. Then the solution obtained is filtered and any solid remaining in the filter is washed with one or more of the above mentioned solvents.

The filtrate obtained by the process described above is added slowly, preferably dropwise, to an organic solvent which is heated to a temperature of >40°C, preferably above 60°C, most preferably to boiling point. The solvent

used is preferably an organic aprotic solvent, more preferably an organic, aprotic and non-polar solvent. Solvents which may be used according to the invention are, most preferably, toluene, chloroform, dichloromethane, tetrahydrofuran, diethylether, diisopropylether, methyl-tert. butylether, acetone, methylisobutylketone, benzene or acetonitrile, of which toluene, benzene and methylisobutylketone are particularly preferred. The solvent toluene is of exceptional importance according to the invention. At the same time as the filtrate is added to the heated solvent, in a preferred embodiment of the invention, some of the solvent is distilled off (optionally azeotropically). After all the filtrate has been added, more solvent (e.g. about one to two thirds of the total amount of solvent added by this stage) may optionally be removed by distillation.

The concentrated solution thus obtained is cooled, preferably to ambient temperature, whereupon the telmisartan sodium salt crystallises out. After crystallisation is complete the crystals are separated off, optionally washed with the organic solvent mentioned above and finally dried.

The crystalline telmisartan sodium salt according to the invention may also be obtained starting from the acid addition salts of formula **2**



x H-X

2

wherein H-X denotes an acid selected from among hydrochloric acid, hydrobromic acid, toluenesulphonic acid or methanesulphonic acid. Of the above mentioned acid addition salts of formula **2** the salt wherein H-X denotes hydrochloric acid is of particular significance. This acid addition salt is also referred to hereinafter as telmisartan hydrochloride.

The compounds of formula **2** may be obtained for example from *tert.*-butyl 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate (=tert.-butyl ester of telmisartan) known from the prior art by saponification in acetic acid in the presence of the acid H-X.

In order to prepare the crystalline telmisartan sodium salt of formula **1** according to the invention starting from the acid addition salts of formula **2** the following procedure may be used, according to the invention.

The compound of formula **2** is taken up in a suitable solvent and combined with a suitable sodium salt.

The solvent may be water and/or a suitable alcohol, such as methanol, ethanol or isopropanol mixed with an aprotic organic solvent selected from among toluene, chloroform, dichloromethane, tetrahydrofuran, diethylether, diisopropylether, methyl-tert. butylether, acetone, methylisobutylketone, benzene and acetonitrile. It is particularly preferred to use, as the solvent, water mixed with ethanol or isopropanol mixed with an aprotic organic solvent selected from among toluene, benzene and methylisobutylketone, most preferably toluene. A mixture of water, isopropanol and toluene has proved particularly suitable for this step of the synthesis.

The amount of solvent or solvent mixture used depends on the amount of acid addition salt **2** used. Preferably, about 0.3 – 3.5 L, preferably about 1 – 2.5 L, more preferably about 1.5 - 2 L of the above mentioned solvent or solvent mixture are used per mol of compound **2** used. If the solvent used is the preferred solvent mixture according to the invention which contains an alcohol as the third solvent component in addition to water and an aprotic organic solvent, the ratios by volume of water to aprotic organic solvent according to the invention are preferably in a range from 1:5 to 1:50 and the ratio of water to alcohol used is in a range from 2:1 to 1:40. Preferably, in a solvent mixture of this kind, the ratios of water to aprotic organic solvent are in the range from 1:10 to 1:30, preferably in the range from 1:15 to 1:25 and the ratio of water to alcohol used is in a range from 1:1 to 1:20, preferably in the range from 1:5 to 1:15.

Preferably, the solvent or solvent mixture mentioned above contains about 10 to 100 ml of water, preferably about 30 to 80 ml of water, most preferably about 40 to 70 ml of water, per mol of **2**. Preferably the solvent or solvent mixture used also contains about 100 to 1000 ml of alcohol, preferably about 300 to 800 ml alcohol, most preferably about 400 to 700 ml alcohol, per mol of **2**. Finally, the solvent or solvent mixture used preferably contains as the third

component of the solvent, about 200 to 2000 ml of the above mentioned aprotic organic solvent, preferably about 600 to 1600 ml, most preferably about 800 to 1400 ml of the above mentioned aprotic organic solvent, per mol of **2**.

Suitable sodium salts which may be used for reacting **2** to **1** include sodium hydroxide, sodium hydride, sodium carbonate, sodium hydrogen carbonate or sodium alkoxides. By sodium alkoxides are meant the sodium salts which are formed with lower alcohols, preferably with alcohols selected from among methanol, ethanol, isopropanol, n-propanol, tert-butanol, sec.-butanol, isobutanol, n-butanol and tert.-amylalcohol. Of particular interest according to the invention are sodium salts selected from among sodium hydroxide, sodium hydride, sodium ethoxide and sodium methoxide, while the sodium alkoxides sodium ethoxide and sodium methoxide, particularly sodium methoxide are of particular importance according to the invention for this reaction step. The above mentioned sodium salts may be added to the reaction mixture as solids. In the case of sodium methoxide however it is preferable to add it in the form of a methanolic solution. Methanolic solutions of sodium methoxide which contain it in a concentration of at least 10%, most preferably about 20-40 % (w/w) , are particularly preferred. For example, the methanolic sodium methoxide solution used may have a concentration of about 30 wt.%.

The amount of sodium salt to be used is naturally dependent on the amount of free acid telmisartan used. According to the invention, at least 2 mol of sodium salt have to be added per mol of telmisartan acid addition salt of formula **2** used. According to the invention it is also possible to add an excess of sodium salt.

It may be useful in some cases to add activated charcoal to the above mentioned reaction mixture. For example, it may be added in an amount of about 5 - 50 g per mol of **2** used, preferably in an amount of about 10 - 40 g per mol of **2** used.

After the sodium salt and optionally the activated charcoal has been added the reaction mixture obtained is heated to a temperature of about 50-100°C, preferably about 60-90°C, most preferably about 70-80°C for a period of about 10 minutes to 2 hours, preferably for about 20-45 minutes. In the course of

this heating, some of the solvent, preferably about 10-50%, most preferably about 20-40% of the total quantity of solvent may be distilled off.

The remaining suspension is then filtered, the filter residue is optionally washed with one of the above mentioned aprotic organic solvents, preferably with the aprotic organic solvent which is also used in the reaction.

The filtrate obtained is then diluted with a solvent or mixture of solvents. It is preferable to use a mixture of water and the above mentioned aprotic organic solvent for this. Preferably, at this point, about 10 to 100 ml of water, preferably about 30 to 80 ml of water, most preferably about 40 to 70 ml of water are used per mol of the compound **2** originally used. At this point, 250 to 3000 ml, preferably about 800 to 2000 ml, most preferably about 1200 to 1800 ml of aprotic organic solvent are used per mole of the compound **2** originally used.

After dilution, the mixture obtained is refluxed. Then about 1-2 L, preferably about 1200 to 1800 ml of solvent are distilled off per mole of the compound **2** originally used. After the solvent has been distilled off the telmisartan-sodium salt **1** according to the invention crystallises out. The crystals obtained are isolated, optionally washed with one of the above mentioned aprotic organic solvents and finally dried.

Crystalline telmisartan-sodium salt may also be obtained by the methods described above in the form of the solvates or hydrates thereof, preferably in the form of the hydrates thereof, most preferably in the form of the hemihydrate.

In view of the pharmaceutical activity of the crystalline telmisartan sodium salt according to the invention, it is used for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition for the prevention or treatment of diseases wherein the administration of therapeutically effective doses of one or more angiotensin-II-antagonists may provide a therapeutic benefit. Preferably, the present invention relates to the use of crystalline telmisartan-sodium salt for preparing a pharmaceutical composition for the prevention or treatment of diseases selected from among hypertension, cardiac insufficiency, ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), myocardial infarct, the progression of cardiac

insufficiency after myocardial infarct, the prevention of cardiovascular deaths, stroke, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, glaucoma, gastrointestinal diseases and bladder diseases, the prevention or treatment of hypertension, cardiac insufficiency, myocardial infarct and stroke and the prevention of cardiovascular deaths being particularly preferred.

Accordingly, the present invention is directed to a pharmaceutical composition characterised in that it contains telmisartan-sodium salt optionally combined with other active substances such as diuretics.
For this purpose the active substance or substances are generally formulated with one or more excipients such as mannitol, sorbitol, xylitol, saccharose, calcium carbonate, calcium phosphate, lactose, croscarmellose sodium salt (cellulose carboxymethylether sodium salt, cross-linked), crospovidone, sodium starch glycolate, hydroxypropylcellulose (low-substituted), maize starch, polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives (copovidone), hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose or starch, magnesium stearate, sodium stearylfumarate, talc, hydroxypropylmethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

In a pharmaceutical composition containing the telmisartan sodium salt as the sole active substance, one or more excipients such as sorbitol, xylitol, saccharose, croscarmellose sodium salt, crospovidone, sodium starch glycolate, hydroxypropylcellulose, polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives (copovidone), hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose or sodium stearylfumarate, hydroxypropylmethylcellulose, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetylstearylalcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof may be used, in particular. Corresponding tablets may be obtained for example by mixing the active substance or substances with one or more excipients and subsequently compressing them. Examples of excipients are

- inert diluents such as mannitol, sorbitol, xylitol, saccharose, calcium carbonate, calcium phosphate and lactose;
- disintegrants such as croscarmellose sodium salt (cellulose carboxymethylether sodium salt, cross-linked), crospovidone, sodium starch glycolate, hydroxypropylcellulose (low-substituted) and maize starch;
- binders such as polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives (copovidone), hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose or starch;
- lubricants such as magnesium stearate, sodium stearyl fumarate and talc;
- agents for achieving delayed release such as hydroxypropylmethylcellulose, carboxymethylcellulose, cellulose acetate phthalate and polyvinyl acetate; and
- pharmaceutically permitted colourings such as coloured iron oxides.

The tablets may also consist of several layers.

The properties of tablets may sometimes also be influenced by granulating individual components and active substances before they are compressed and only then compressing them with other excipients.

Particularly suitable excipients for the direct compression of the telmisartan sodium salt as the active substance on its own or together with the diuretic hydrochlorothiazide are sorbitol and magnesium stearate, while these excipients may optionally be replaced by other excipients suitable for direct tabletting such as mannitol or saccharose. In order to differentiate visually between tablets with different compositions of active substances it is useful to make these tablets in different colours. For this purpose colouring excipients such as coloured iron oxides or other pharmaceutically permitted colourings may be added before the compression process.

Particularly good solubility characteristics of the active substances are obtained in tablets which have been prepared by granulating the telmisartan sodium salt in a dry granulation process before the compression to form tablets. The salt is mixed for example with mannitol, hydroxypropylcellulose and optionally a colouring excipient such as red iron oxide in suitable mixers, then screened and finally subjected to dry granulation in a roller compactor, for example. The excipients mentioned may be replaced for example by excipients such as lactose or microcrystalline cellulose. The granules

obtained are then optionally mixed with another active substance such as hydrochlorothiazide as well as with excipients such as mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and optionally a colouring excipient such as red iron oxide in a suitable mixer and finally pressed into tablets. Alternatively, excipients such as lactose or croscarmellose sodium salt (cellulose carboxymethylether sodium salt, cross-linked) may also be used.

The content of telmisartan sodium salt is usually 60-90 mg, 30-60 mg or 15-30 mg of the salt per tablet, coated tablet or capsule. Amounts of 80-85 mg, 40-45 mg or 20-25 mg are preferred. These amounts correspond roughly to a content of 80 mg, 40 mg and 20 mg, respectively, of the free acid telmisartan. If these formulations also contain hydrochlorothiazide, it is present in each tablet, coated tablet or capsule in an amount of 10-15 mg or 20-30 mg, preferably 12-13 mg or 24-26 mg. Processes for preparing the above mentioned pharmaceutical compositions, particularly those wherein the active substances are compressed into tablets, are also a subject of the present invention.

Pharmaceutical active substances which may optionally be incorporated into formulations together with the telmisartan sodium salt are

- diuretics such as hydrochlorothiazide;
- antihypertensives such as
  - -- ACE inhibitors (e.g. captopril, enalapril, lisinopril, ramipril and perindopril);
  - -- angiotensin receptor antagonists (e.g. candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan);
  - -- calcium antagonists (e.g. nifedipin and verapamil); or
  - -- alpha- or beta-receptor blockers (e.g. ergotamine, dihydroergotamine, atenolol, acebutolol, metoprolol, propranolol and pindolol);
- antidiabetics such as nateglinide, repaglinide and metformin;
- thrombocyte aggregation inhibitors such as clopidogrel, acetylsalicylic acid or dipyridamole;
- vasodilators such as minoxidil;
- lipid or cholesterol lowering agents such as procubol, sitosterol, MTP inhibitors, HMG-CoA-reductase inhibitors such as lovastatin, simvastatin and atorvastatin or fibrates.

The example of synthesis that follows serves to illustrate a method of preparing crystalline telmisartan-sodium salt carried out by way of example. It is intended solely as a possible procedure provided by way of example, without restricting the invention to its contents.

Synthesis Example 1: Preparation of crystalline telmisartan-sodium salt starting from telmisartan:

The starting material used to prepare crystalline telmisartan-sodium salt according to the invention may be the free acid, which may be obtained by methods known from the prior art (e.g. according to EP 502314 A1).
154.4 g of telmisartan are placed in 308.8 ml of toluene in a suitable reaction vessel. The suspension is combined with 27.8 g of 44.68% sodium hydroxide solution and 84.9 ml of ethanol and heated to 78°C for about 30 min, then the mixture is filtered. If desired, if large amounts of solid are left in the filter, this may be washed with a mixture of 61.8 ml of toluene and 15.3 ml of ethanol.

463.2 ml of toluene are placed in another reaction vessel and refluxed. The filtrate obtained by the process described above is slowly added dropwise thereto at boiling temperature and simultaneously distilled off azeotropically. After it has all been added any solution which may have been obtained from washing the filter is also added and again distilled off azeotropically. The mixture is distilled at up to 103°C and the suspension is allowed to cool to ambient temperature. The crystals are suction filtered, washed with 154.4 ml of toluene and dried at 60°C in the circulating air drier.

Yield: 154.6 g (96%) of colourless crystals;

$C_{33}H_{29}N_4O_2Na \times 0.5H_2O$	calc.:	C 72.51	H 5.72	N 10.25
	found:	C 72.57	H 5.69	N 10.21

Synthesis Example 2: Preparation of crystalline telmisartan-sodium salt starting from telmisartan hydrochloride:

A) Preparation of telmisartan-hydrochloride:

411 g of *tert.*-butyl 4′-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate are suspended in 822 ml of glacial acetic acid and combined with 213 g of concentrated aqueous

hydrochloric acid (37%). The mixture is refluxed and about 640 ml of solvent are distilled off. The residue remaining is slowly combined with about 620 ml of water at 50-60°C. To this mixture are added 20 g of activated charcoal (e.g. Norit SX 2 Ultra) and the resulting mixture is stirred for about 10 min at constant temperature. After filtering, the residue is washed three times with 25 ml of glacial acetic acid and about 620 ml of water. The filtrate obtained is again heated to about 50-60°C and about 2 L of water are added. After stirring for about 12 hours at about 23°C the crystals formed are suction filtered and washed twice with about 500 ml of water, once with about 900 ml of acetone and then dried at about 60°C.

Yield: 367 g (92.5%), colourless crystals, melting point: = 278°C

B) Preparation of crystalline telmisartan sodium salt from telmisartan hydrochloride

55.1 g of telmisartan hydrochloride are taken up in 110.2 ml of toluene, 5.5 ml of water, 55.1 ml of isopropanol and this mixture is combined with 36.9 g of sodium methoxide (30% in methanol) and 2.75 g of activated charcoal (e.g. Sorit SX 2 Ultra). The mixture is then heated to about 75°C, and about 50 ml of solvent mixture are distilled off at constant temperature over about 30 min. The suspension obtained is filtered and the residue is washed with about 20 ml of toluene. The filtrate is combined with about 5 ml of water and about 150 ml of toluene. The mixture obtained is refluxed. During this time about 150 ml of solvent mixture are azeotropically distilled off (at up to 102°C). The mixture is left to crystallise for one hour at 100°C. The crystals are suction filtered, washed with about 50 ml of toluene and dried at about 60°C.

Yield: 53.6 g (99%), colourless crystals ;

$C_{33}H_{29}N_4O_2Na \cdot 0.5H_2O$	calc.:	C 72.51	H 5.72	N 10.25
	found:	C 72.44	H 5.68	N 10.20

To prepare a pharmaceutical composition containing the active substance, particularly an orally administered pharmaceutical composition, most preferably a tablet, procedures known in the art may be used.
Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as mannitol, sorbitol, xylitol, saccharose, calcium carbonate, calcium phosphate or lactose, disintegrants such as croscarmellose sodium salt (cellulose

carboxymethylether sodium salt, cross-linked), crospovidone, sodium starch glycolate, hydroxypropylcellulose (low-substituted) or maize starch, binders such as polyvinylpyrrolidone, copolymers of vinylpyrrolidone with other vinyl derivatives (Copovidone), hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose or starch, lubricants such as magnesium stearate, sodium stearyl fumarate or talc and/or agents for obtaining delayed release, such as hydroxypropylmethylcellulose, carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

The following are some examples of pharmaceutical preparations which may be used according to the invention. They are intended purely as illustrations by way of example without restricting the subject matter of the invention thereto.

Formulation Example 1: Tablet 1

Ingredients:	mg
Telmisartan-sodium salt	83.417
Mannitol	299.083
Microcrystalline Cellulose	100.000
Croscarmellose sodium salt	10.000
Magnesium stearate	7.500
Total	500.000

Formulation Example 2: Tablet 2

Ingredients:	mg
Telmisartan-sodium salt	83.417
Sorbitol	384.083
Polyvidone K25	25.000
Magnesium stearate	7.500
Total	500.000

Formulation Example 3: Tablet 3

Ingredients:	mg
Telmisartan-sodium salt	41,708
Mannitol	149,542
Microcrystalline Cellulose	50,000
Croscarmellose sodium salt	5,000
Magnesium stearate	3,750
Total	250,000

Formulation Example 4:

By directly compressing the telmisartan sodium salt with the excipients sorbitol and magnesium stearate tablets are obtained whose concentration of active substance corresponds to an amount of 80 mg, 40 mg and 20 mg of free acid of telmisartan.

Tablet containing the **equivalent** of **80 mg** of free acid telmisartan:

Ingredient	**mg/Tablet**	**%Tablet**
Telmisartan sodium salt	83.417	17.379
Sorbitol	389.383	81.121
Magnesium stearate	7.200	1.500
Total	**480.000**	**100.000**

Shape: oval
Dimensions: 16.2 x 7.9 mm

Tablet containing the **equivalent** of **40 mg** of free acid telmisartan:

Ingredient	**mg/Tablet**	**%Tablet**
Telmisartan sodium salt	41.708	17.378
Sorbitol	194.692	81.122
Magnesium stearate	3.600	1.500
Total	**240.000**	**100.000**

Shape: oval
Dimensions: 12 x 5.9 mm

Tablet containing the **equivalent** of **20 mg** of free acid telmisartan:

Ingredient	**mg/Tablet**	**%Tablet**
Telmisartan sodium salt	20.854	17.378
Sorbitol	97.346	81.122
Magnesium stearate	1.800	1.500
Total	**120.000**	**100.000**

Shape: round
Dimensions: 7 mm

Formulation Example 5:

The telmisartan sodium salt is first mixed with mannitol, red iron oxide and hydroxypropylcellulose in an intensive mixer ("High-Shear Mixer"). Then magnesium stearate is added by sifting through a 0.8 mm screen and the mixture is subjected to dry granulation in a roller compactor. In parallel, hydrochlorothiazide is mixed with mannitol, microcrystalline cellulose, sodium glycol starch and red iron oxide in an intensive mixer. Both this mixture and the granulated telmisartan sodium salt are sieved through a 0.8 mm screen, mixed together in a free fall blender and finally subjected to a last mixing process with magnesium stearate screened through a 0.8 mm screen. A composition is obtained which can be compressed without any problems and the tablets produced from it exhibit good solubility for the active substances. This composition of active substances and excipients is compressed with a suitable tablet press (e.g. Korsch EK0 or Fette P1200). Tablets of the following composition are prepared, the amount of telmisartan sodium salt contained in each tablet corresponding to an amount of 80 mg of the free acid of telmisartan.

Ingredient	mg/Tablet	%Tablet
Telmisartan sodium salt	83.417	13.903
Hydrochlorothiazide	12.500	2.083
Mannitol	336.483	56.081
Cellulose microcrystalline	120.000	20.000
Sodium glycol starch	30.000	5.000
Red iron oxide	0.600	0.100
Hydroxypropylcellulose	5.000	0.833
Magnesium stearate	12.000	2.000
Total	**600.000**	**100.000**

The composition of the tablet may also be as follows:

Ingredient	mg/Tablet	%/Tablet	%/Granules
Telmisartan sodium salt	83.417	13.903	83.417
Mannitol	10.983	1.831	10.983
Hydroxypropylcellulose	5.000	0.833	5.000
Red iron oxide	0.100	0.017	0.100
Magnesium stearate	0.500	0.083	0.500
Total	**100.000**	**16.667**	**100.000**
Hydrochlorothiazide	12.500	2.083	
Mannitol	325.500	54.250	
Cellulose microcrystalline	120.000	20.000	
Sodium glycol starch	30.000	5.000	
Red iron oxide	0.500	0.083	
Magnesium stearate	11.500	1.917	
Total	**600.000**	**100.000**	

The tablets have the following properties:
Dimensions: 16.2 x 7.9 mm (r=5.86 mm)
Weight: 598.7 mg ± 0.22 %
Thickness: on average 6.16 mm
Breaking strength: on average 145 N
Abrasion: 0.09 %
Decomposition time: on average 153 s

95 ± 3.1 % of the telmisartan sodium salt dissolve after 30 minutes in 900 ml of 0.1 M phosphate buffer, pH 7.5, with stirring (75 rpm). 88 ± 3.8 % hydrochlorothiazide dissolve after 30 minutes in 900 ml of 0.1 M HCl (100 rpm).

Formulation Example 6:

Hydrochlorothiazide, telmisartan sodium salt, sorbitol and red iron oxide are mixed in a free fall blender, passed through a 0.8 mm screen and, after the addition of magnesium stearate, processed in a free fall blender to form a powdered mixture.

This composition of active substances and excipients is then compressed into tablets using a suitable tablet press (e.g. Korsch EK0 or Fette P1200). Tablets of the following composition are prepared, the amount of telmisartan sodium salt contained in each tablet corresponding to an amount of 80 mg of the free acid of telmisartan.

Ingredient	**mg/Tablet**	**%**
Telmisartan sodium salt	83.417	13.903
Hydrochlorothiazide	12.500	2.083
Sorbitol	494.483	82.414
Red iron oxide	0.600	0.100
Magnesium stearate	9.000	1.500
Total	**600.000**	**100.000**

The tablets of three batches have the following properties:

Batch 1:
Dimensions: 16.2 x 7.9 mm (r=5.86 mm)
Weight: 600.7 mg ± 0.34 %
Thickness: on average 5.96 mm
Breaking strength: on average 142 N
Abrasion: 0.12 %
Decomposition time: on average 304 s

Batch 2:

Dimensions: 16.2 x 7.9 mm (r=5.86 mm)
Weight: 600.6 mg ± 0.28 %
Thickness: on average 6.11 mm
Breaking strength: on average 115 N
Abrasion: 0.17 %
Decomposition time: on average 331 s

Batch 3:
Dimensions: 16.2 x 7.9 mm (r=5.86 mm)
Weight: 591.1 mg ± 0.56 %
Thickness: on average 5.89 mm
Breaking strength: on average 116 N
Abrasion: 0.13 %
Decomposition time: on average 416 s

The telmisartan sodium salts of the tablets from the three batches dissolves after 30 minutes' stirring (75 rpm) in 900 ml of 0.1 M phosphate buffer pH 7.5 at 92 ± 1.5 %, 96 ± 1.8 % and 100 ± 1.0 %, respectively. The hydrochlorothiazide dissolved after 30 minutes in 900 ml of 0.1 M HCl (100 rpm) at 69 ± 6.3 %, 72 ± 2.1 % and 78 ± 1.8 %, respectively.

Abstract

The invention relates to a pharmaceutical formulation of the crystalline sodium salt of 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid (telmisartan), and to processes for the preparation thereof.